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ORIGINAL ARTICLE

Prostate Cancer

Prostate-specific antigen density predicts favorable pathology and biochemical recurrence in patients with intermediate-risk prostate cancer

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This study was designed to identify clinical predictors of favorable pathology and biochemical recurrence (BCR) in patients with intermediate-risk prostate cancer (IRPCa). Between 2006 and 2012, clinicopathological and oncological data from 203 consecutive men undergoing robot-assisted radical prostatectomy (RARP) for IRPCa were reviewed in a single-institutional retrospective study. Favorable pathology was defined as Gleason score ≤6 and organ-confined cancer as detected by surgical pathology. Logistic regression analysis was used to determine predictive variables of favorable pathology, and the Kaplan–Meier and multivariate Cox regression model were used to estimate BCR-free survival after RARP. Overall, 38 patients (18.7%) had favorable pathology after RARP. Lower quartile prostate-specific antigen density (PSAD) was associated with favorable pathology compared to the highest quartile PSAD after adjusting for preoperative PSA, clinical stage and biopsy Gleason score (odds ratio, 5.42; 95% confidence interval, 1.01–28.97; *P* = 0.048). During a median 37.8 (interquartile range, 24.6–60.2) months of follow-up, 66 patients experienced BCR. There were significant differences with regard to BCR free survival by PSAD quartiles (log rank, *P* = 0.003). Using a multivariable Cox proportion hazard model, PSAD was found to be an independent predictor of BCR in patients with IRPCa after RARP (hazard ratio, 4.641; 95% confidence interval, 1.109–19.417; *P* = 0.036). The incorporation of the PSAD into risk assessments might provide additional prognostic information and identify some patients in whom active surveillance would be appropriate in patients with IRPCa.

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INTRODUCTION

Prostate cancer (PCa) is the most common solid organ malignancy in men in many western countries including the United States and is the fifth most common in Korean males.[1–3] PCa shows an extremely heterogeneous clinical course, ranging from indolent and organ-confined to aggressive, metastatic lethal disease, leading to the overtreatment of men with relatively indolent disease and the undertreatment of those with aggressive tumors.[4,5] Consequently, there is a great need to accurately assess the tumor characteristics of PCa so that appropriate treatment options can be considered.

Currently, pathological analyses (including clinical stage and tumor grade in biopsy as measured by the Gleason score) and serum prostate-specific antigen (PSA) levels are key determinants for risk assessment and therapeutic decision-making.[6] However, none of the histological criteria or biomarkers reported to date show sufficient sensitivity or specificity for detecting, monitoring, and determining the prognosis of PCa. D'Amico *et al.*[7] were the first to combine the use of preoperative PSA levels, clinical stage, and biopsy Gleason score to stratify patients with PCa into low-, intermediate-, and high-risk groups. Even within a given risk group, significant clinical heterogeneity remains, particularly for those with intermediate-risk PCa (IRPCa).[8,9] Biochemical recurrence (BCR) rates following definitive primary treatment for IRPCa are variable, with 5-year rates ranging from 2% to 70%.[10,11] Given this clinical heterogeneity, a uniform treatment paradigm is unlikely to be an optimal approach for IRPCa. The optimal treatment for IRPCa is controversial; radical surgery, brachytherapy, external beam radiotherapy, hormone suppression, and combinations of these modalities are all feasible treatment options.[12] Recently, several investigators have reported the appropriateness of active surveillance (AS) in select men with IRPCa, demonstrating favorable outcomes.[13,14] Thus, there is a critical need for methods capable of precise risk stratification and identifying some patients in whom AS would be appropriate in patients with IRPCa. To address these issues, we investigated preoperative variables associated with favorable pathology and BCR after RARP in IRPCa.

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MATERIALS AND METHODS

We retrospectively reviewed the data of 1086 patients who underwent robot-assisted radical prostatectomy (RARP) for PCa at Severance Hospital between January 2006 and December 2012. Of the total RARP cases, 19.6% of patients ($n = 213$) met the criteria of IRPCa according to the D'Amico classification, defined as clinical stage T2b or PSA levels between 10 and 20 or Gleason score of 7. Patients who received neo-adjuvant treatment ($n = 8$) or adjuvant radiotherapy ($n = 6$, four patients also received neo-adjuvant treatment) were excluded. As a result, 203 subjects satisfied the final inclusion criteria.

RARP was carried out using our standardized extraperitoneal technique by a single surgeon (YDC).[15] The study was carried out in agreement with applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. The Institutional Review Board of the hospital approved the present study protocol (Approval number: 4-2014-0619). Favorable pathology was defined as a Gleason score ≤6 and organ-confined cancer as detected by surgical pathology. BCR was defined as two sequential PSA values ≥0.2 ng ml^{-1} after prostatectomy.

Continuous variables are shown as the median and IQR. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Mann–Whitney U-test. The Fisher exact test was used to evaluate the association between categorical variables. PSAD was categorized into approximate quartiles within the nested subcohort, with the highest quartile assigned as the reference group. Survival analyses were conducted according to the Kaplan–Meier method, and survival characteristics were compared using the log-rank test. Univariate and multivariate Cox regression model was used to identify the independent prognostic factors for BCR following RARP. Variables of $P < 0.1$ on univariate analysis included in the multivariate analysis. Statistical significance was considered at $P < 0.05$, and all reported P values are two-sided. Analysis was performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

Table 1 lists the baseline characteristics of the 203 IRPCa cases. The median prebiopsy PSA and PSAD were 7.92 (IQR 5.59–11.93) ng ml^{-1} and 0.27 (IQR 0.19–0.38) ng ml^{-1} g^{-1}, respectively. The majority of men had a biopsy Gleason score 7 (69.9%); of those, 65 patients had a primary Gleason pattern of 4.

After RARP, pathologic organ-confined disease was found in 103 (50.7%) cases and Gleason scores ≤6, 3 + 4, 4 + 3, and ≥8 were found in 53 (26.1%), 76 (37.4%), 60 (29.6%), and 14 (6.9%) cases, respectively. Overall, 38 patients (18.7% of IRPCa cohort) had favorable pathology after RARP (**Table 1**).

Table 1: Baseline characteristics of patients and pathological outcomes on radical prostatectomy

Characteristics	*Value (range or percentage)*
Baseline characteristics	
Patients (*n*)	203
Follow-up period, months (median)[a]	37.8 (24.6–60.2)
Age, years (mean)[a]	65.0 (60.0–70.0)
BMI, kg m^{-2} (median)[a]	24.2 (22.4–25.6)
PSA, ng ml^{-1} (median)[a]	7.92 (5.59–11.93)
PSAD, ng ml^{-1} cm^{-3} (median)[a]	0.27 (0.19–0.38)
Biopsy Gleason score, *n* (%)	
5	2 (1.0)
6	59 (29.1)
7 (3+4)	77 (37.9)
7 (4+3)	65 (32.0)
Clinical T stage, *n* (%)	
T1c	93 (45.8)
T2a	73 (36.0)
T2b	37 (18.2)
Pathological outcomes, *n* (%)	
High-grade PIN	120 (59.1)
Lymphovascular invasion	10 (4.9)
Perineural invasion	113 (59.1)
Gleason score, *n* (%)	
5	1 (0.5)
6	52 (25.6)
7 (3+4)	76 (37.4)
7 (4+3)	60 (29.6)
8	9 (4.4)
9	5 (2.5)
Pathologic T stage, *n* (%)	
T2a	25 (12.3)
T2b	13 (6.4)
T2c	65 (32.0)
T3a	88 (43.3)
T3b	9 (4.4)
T4	3 (1.5)
Positive surgical margin, *n* (%)	53 (26.1)
Favorable pathology[b], *n* (%)	38 (18.7)

[a]The data are shown as mean or median (IQR); [b]Favorable pathology was defined as Gleason score ≤6 and organ-confined cancer as detected by surgical pathology. BMI: body mass index; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; PIN: prostatic intraepithelial neoplasia; IQR: interquartile range

Clinical variables associated with favorable pathology in patients with IRPCa

Preoperative PSAD and CAPRA score were significantly associated with favorable pathology after RARP ($P = 0.017$, $P = 0.013$, respectively). However, there were no significant differences among the favorable and unfavorable pathology groups with respect to other preoperative variables, including age, BMI, preoperative PSA, and clinical stage and grade (**Table 2**).

When PSAD was categorized into quartiles, the lower quartile PSAD group was associated with favorable pathology compared with the highest quartile PSAD group after adjusting for PSA, clinical stage, and biopsy Gleason score (odds ratio, 5.42; 95% confidence interval [CI], 1.01–28.97; $P = 0.048$) (**Table 3**).

Prediction of BCR after radical prostatectomy in patients with IRPCa

During a median 37.8 (interquartile range 24.6–60.2) months of follow-up, 66 patients (32.5% of the IRPCa cohort) experienced BCR and the majority of BCR (95.5%) were occurred in unfavorable pathology group. One- and 3-year BCR-free survival rates were 94.6% and 91.8% for patients with favorable pathology, whereas 78.9% and 63.9% for patients with unfavorable pathology.

Kaplan–Meier analysis exhibits significantly different BCR-free survival by PSAD quartiles (log-rank $P = 0.003$) (**Figure 1**). **Table 4** shows results from univariate and multivariate Cox proportion hazard analysis for prediction of BCR after RARP. In univariate analyses, lower preoperative PSA, PSAD, CAPRA score, LVI and positive surgical margins were associated with BCR after RARP. When multivariate analysis with PSAD, PSAD (hazard ratio [HR], 4.641; 95%

CI, 1.109–19.417; P = 0.036), LVI (HR, 3.734; 95% CI, 1.644–8.482; P = 0.002) and positive surgical margins (HR, 1.842; 95% CI, 1.108–3.061; P = 0.018) were independent predictors of BCR after RARP.

DISCUSSION

The current study investigated the preoperative variables of favorable pathology and the risk of BCR in patients with IRPCa. Our study showed that approximately 20% of patients with IRPCa had a favorable pathology as detected by final pathology. Preoperative PSAD was not only associated with favorable pathology, but also an independent predictor of BCR in patients with IRPCa after prostatectomy. PSAD might be an additional tool for stratifying men with IRPCa and identifying some patients in whom AS would be appropriate in this setting.

PCa shows an extremely heterogeneous clinical course, ranging from indolent and organ-confined to aggressive, metastatic lethal disease.[16–18] Moreover, we acknowledge that patients in each risk group have significant clinical heterogeneity, particularly IRPCa.[8,9] The original research concerning within-group heterogeneity by Reese *et al*.[9] revealed heterogeneous pathologic and biochemical outcomes among men within a single NCCN risk group. In their study, BCR-free survival rates were superior in men classified as intermediate-risk by clinical stage compared with those assigned by biopsy Gleason score or PSA level. Interestingly, comparing men who met only one intermediate-risk criterion with low-risk men, no significant differences were found in terms of 10-year BCR-free survival by clinical stage. These authors also found that the BCR-free survival rates also differed according to the number of intermediate-risk criteria. Additional clinical factors have been proposed for stratifying men with IRPCa, including the proportion of positive biopsy cores, pretreatment PSA velocity, and primary Gleason pattern.[19–21] Series from the Mayo Clinic and Johns Hopkins University showed a statistically significant difference in biochemical and progression-free outcomes in patients with a total Gleason score of 7, when stratified according to primary Gleason pattern.[22,23] Recently, Zumsteg *et al*.[8] proposed a new risk stratification system for patients with IRPCa treated with dose-escalated, external-beam radiation therapy. They defined unfavorable IRPCa as any intermediate-risk patient with a primary Gleason pattern of 4, percentage of positive biopsy cores greater than or equal to 50%, or multiple intermediate-risk factors. Despite being significantly more likely to receive ADT, patients classified with unfavorable IRPCa had worse BCR-free survival, local failure, distant metastases, and CSM than patients with favorable IRPCa. Similarly, our study cohorts showed heterogeneous pathologic outcomes. Although 18.7% of the entire cohort had a favorable outcome after radical prostatectomy, a significant proportion of patients showed a high-grade advanced stage of disease.

Table 2: Comparison of preoperative variables between pathologic favorable and unfavorable group after radical prostatectomy

Variables	*Favorable pathology*		*P*
	Yes	*No*	
Patients, *n* (%)	38 (18.7)	165 (81.3)	
Preoperative variables			
Age, years (mean)[a]	63.9 (60.0–70.0)	65.3 (60.0–71.0)	0.252*
BMI, kg m^{-2} (median)[a]	24.5 (22.3–26.2)	24.2 (22.5–25.5)	0.310*
PSA, ng ml^{-1} (median)[a]	7.98 (4.70–11.56)	7.92 (6.03–11.98)	0.134*
PSAD, ng ml^{-1} cm^{-3} (median)[a]	0.23 (0.12–0.30)	0.28 (0.21–0.39)	0.017*
Biopsy Gleason score, *n* (%)			
5	0 (0.0)	2 (1.2)	0.549[†]
6	13 (34.2)	46 (27.9)	
7 (3+4)	16 (42.1)	61 (37.0)	
7 (4+3)	9 (23.7)	56 (33.9)	
Clinical T stage, *n* (%)			
T1c	13 (34.2)	80 (48.5)	0.129[†]
T2a	19 (50.0)	54 (32.7)	
T2b	6 (15.8)	31 (18.8)	
CAPRA score, *n* (%)			
≤2	13 (36.1)	26 (17.2)	0.013[†]
3	15 (41.7)	45 (29.8)	
4	4 (11.1)	29 (19.2)	
5	3 (8.3)	28 (18.5)	
≥6	1 (2.8)	23 (15.2)	

[a]The data are shown as mean or median (IQR). *P* values were obtained from the *Mann–Whitney U-test or [†]Fisher's exact test. PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; CAPRA: cancer of the prostate risk assessment; BMI: body mass index; IQR: interquartile range

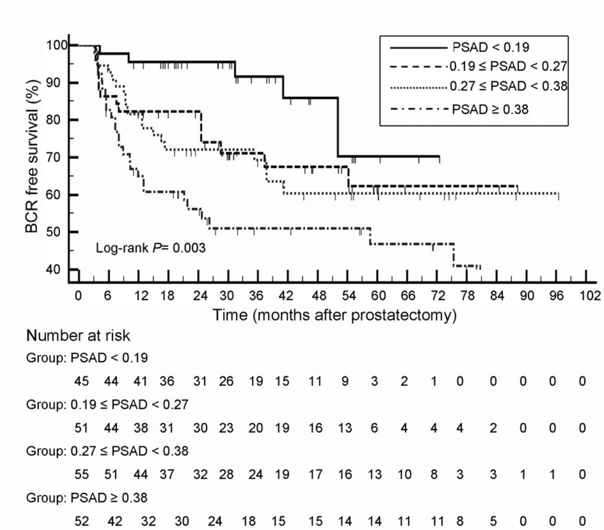

Figure 1: Kaplan–Meier analysis of BCR-free survival categorized by PSAD quartiles in patients with IRPCa; Pairwise analysis, significant between PSAD < 0.19 versus 0.27 ≤ PSAD < 0.38 (P = 0.025), and between PSAD < 0.19 versus PSAD ≥ 0.38 (P < 0.001). BCR: biochemical recurrence; IRPCa: intermediate-risk prostate cancer.

Table 3: Prediction of favorable pathology according to PSAD category in patients with intermediate-risk prostate cancer

PSAD quartile (ng ml^{-1} cm^{-3})	*Patients (n)*	*Favorable pathology[a], n (%)*	*Unfavorable pathology, n (%)*	*OR (95% CI)[b]*	*P*
PSAD<0.19	45	13 (28.9)	32 (71.1)	5.42 (1.01–28.97)	0.048
0.19≤PSAD<0.27	51	9 (17.6)	42 (82.4)	2.27 (0.53–9.63)	0.269
0.27≤PSAD<0.38	55	10 (18.2)	45 (81.8)	2.12 (0.63–7.14)	0.225
PSAD≥0.38	52	6 (11.5)	46 (88.5)	-	

[a]Favorable pathology was defined as Gleason score ≤6 and organ-confined cancer as detected by surgical pathology; [b]ORs were calculated by logistic regression analysis and adjusted for preoperative PSA (continuous), clinical stage (categorical) and biopsy Gleason score (categorical). PSAD: prostate-specific antigen density; CI: confidence interval; OR: odds ratio

Table 4: Univariate and multivariate Cox proportion HR for prediction of biochemical recurrence after radical prostatectomy in patients with intermediate-risk prostate cancer

Parameters	*Univariate analysis*		*Multivariate analysis with PSAD*	
	HR (95%, CI)	*P*	*HR (95%, CI)*	*P*
Preoperative variables				
Age (continuous)	1.024 (0.990–1.059)	0.175		
BMI (continuous)	1.027 (0.932–1.132)	0.590		
PSA (continuous)	1.121 (1.060–1.186)	<0.001	Not applicable	
PSAD (continuous)	6.008 (1.539–23.457)	<0.001	4.641 (1.109–19.417)	0.036
cT stage (≥2a)	1.208 (0.740–1.972)	0.449		
bGS (≥7)	1.117 (0.676–1.848)	0.667		
CAPRA (continuous)	1.233 (1.028–1.479)	0.024	1.173 (0.970–1.418)	0.101
Postoperative variables				
HGPIN (yes)	0.961 (0.538–1.585)	0.876		
LVI (yes)	4.086 (1.833–9.110)	0.001	3.734 (1.644–8.482)	0.002
PNI (yes)	1.405 (0.851–2.321)	0.184		
pT stage (≥3a)	1.558 (0.953–2.549)	0.077	1.181 (0.687–2.030)	0.548
pGS (≥7)	1.730 (0.905–3.306)	0.097	1.199 (0.592–2.429)	0.614
PSM (yes)	2.064 (1.260–3.382)	0.004	1.842 (1.108–3.061)	0.018

PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; HR: hazard ratio; CI: confidence interval; BMI: body mass index; cT: clinical T; bGS: biopsy Gleason score; CAPRA: cancer of the prostate risk assessment; HGPIN: high grade prostatic intraepithelial neoplasia; LVI: lymphovascular invasion; PNI: perineural invasion; pT: pathologic T; pGS: pathologic Gleason score; PSM: positive surgical margin

PSAD was initially introduced to improve the sensitivity and specificity of PSA testing for PCa screening.[24] However, some groups have also examined the role of PSAD in predicting advanced pathology after radical prostatectomy or BCR after local treatment.[25,26] PSAD has been adopted as criteria for AS in men with low-risk PCa. The NCCN and PRIAS AS protocols include PSAD as an inclusion criterion. Furthermore, a recent study showed that PSAD was associated with an upgraded Gleason score of the prostatectomy specimen.[27,28] While it is well-known that PSAD is a useful tool for selecting candidates for AS and prediction of BCR after definitive treatment in low-risk disease, the prognostic implications of PSAD in IRPCa have not yet been sufficiently elucidated. Our results suggest the potential utility of PSAD in predicting the favorable pathology and the risk of recurrence after surgery in IRPCa.

Recently, several investigators have reported the appropriateness of AS in select men with IRPCa, demonstrating favorable outcomes.[13,14] The UCSF group reported that selected men with intermediate-risk features be appropriate candidates for AS, and are not necessarily more likely to progress.[29] Better risk assessment through emerging biomarkers and better integration of clinical predictors could discriminate significant from indolent tumors in men with IRPCa. PSAD might be an additional tool for appropriate selection for AS in IRPCa. Further prospective design is needed to confirm the clinical application of PSAD for AS and consequent oncologic safety assessment in intermediate-risk disease.

Our study has both strengths and limitations. It had a retrospective design, which means that there may have been some sampling bias. However, the RARP data originated at a single institution and a single surgeon, minimizing performance variability within groups and decreasing performance bias. In addition, current study cohort consisted entirely of men treated with RARP. Thus, the prognostic implications of PSAD in IRPCa patients treated with brachytherapy, external beam radiotherapy, hormone suppression, and combinations of these modalities should be validated in future studies.

CONCLUSIONS

PSAD is associated with favorable pathology and is an independent predictor of BCR in patients with IRPCa after surgery. PSAD might be an additional tool for sub-stratifying patients with IRPCa into different prognostic groups and identifying some patients in whom AS would be appropriate in this setting.

AUTHOR CONTRIBUTIONS

HWK, JYL, and YDC conceived and designed the study. HDJ and JKK collected the data. SUJ, JKK, and HWK performed the statistical analyses. HWK, JYL, SUJ, and HDJ drafted the manuscript. KSC, WSH, and YDC participated in the design of the study and critical revision of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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